



King's Research Portal

DOI:

[10.1080/17437199.2017.1298045](https://doi.org/10.1080/17437199.2017.1298045)

Document Version

Publisher's PDF, also known as Version of record

[Link to publication record in King's Research Portal](#)

Citation for published version (APA):

Picariello, F., Hudson, J., Moss-Morris, R., Macdougall, I. C., & Chilcot, J. (2017). Examining the efficacy of social-psychological interventions for the management of fatigue in End-Stage Kidney Disease (ESKD): A systematic review with meta-analysis. *Health Psychology Review*, 11(2), 197-216. DOI: 10.1080/17437199.2017.1298045

Citing this paper

Please note that where the full-text provided on King's Research Portal is the Author Accepted Manuscript or Post-Print version this may differ from the final Published version. If citing, it is advised that you check and use the publisher's definitive version for pagination, volume/issue, and date of publication details. And where the final published version is provided on the Research Portal, if citing you are again advised to check the publisher's website for any subsequent corrections.

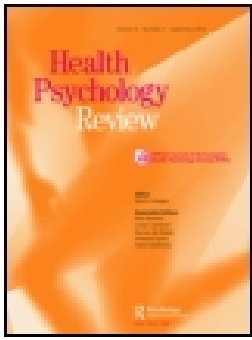
General rights

Copyright and moral rights for the publications made accessible in the Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognize and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the Research Portal

Take down policy

If you believe that this document breaches copyright please contact librarypure@kcl.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.



Examining the efficacy of social-psychological interventions for the management of fatigue in end-stage kidney disease (ESKD): a systematic review with meta-analysis

Federica Picariello, Joanna L. Hudson, Rona Moss-Morris, Iain C. Macdougall & Joseph Chilcot

To cite this article: Federica Picariello, Joanna L. Hudson, Rona Moss-Morris, Iain C. Macdougall & Joseph Chilcot (2017): Examining the efficacy of social-psychological interventions for the management of fatigue in end-stage kidney disease (ESKD): a systematic review with meta-analysis, Health Psychology Review

To link to this article: <http://dx.doi.org/10.1080/17437199.2017.1298045>



© 2017 The Author(s). Published by Informa UK Limited, trading as Taylor & Francis Group



Accepted author version posted online: 01 Mar 2017.
Published online: 06 Mar 2017.



Submit your article to this journal [↗](#)



Article views: 2



View related articles [↗](#)



View Crossmark data [↗](#)

Examining the efficacy of social-psychological interventions for the management of fatigue in end-stage kidney disease (ESKD): a systematic review with meta-analysis

Federica Picariello^a, Joanna L. Hudson^a, Rona Moss-Morris^a, Iain C. Macdougall^b and Joseph Chilcot^a

^aHealth Psychology Section, Psychology Department, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK; ^bDepartment of Renal Medicine, King's College Hospital, London, UK

ABSTRACT

Fatigue affects between 42% and 89% of end-stage kidney disease (ESKD) patients, with significant repercussions on quality of life and clinical outcomes. Fatigue management revolves around pharmacotherapy or exercise, which have only modest and short-term improvements. The aim of this systematic review was to investigate whether social-psychological interventions are effective at reducing fatigue in ESKD. Databases were searched to identify randomized controlled trials (RCTs) and quasi-RCTs that determined the effect of social-psychological interventions on fatigue (primary or secondary outcome), in the renal patient population. A meta-analysis was conducted. Sixteen RCTs ($N = 1536$) were included, predominantly among dialysis patients. Fatigue was a primary outcome in only two studies. The meta-analytic findings showed a significant improvement in fatigue following social-psychological interventions (standardised mean difference, $SMD = 0.37$, $p = .001$; 95% CI 0.15 to 0.59, $I^2 = 69.1\%$, $p < .001$). There was evidence for greater effectiveness of interventions including stress-management/relaxation techniques, evaluated among fatigued samples meeting diagnostic thresholds, against passive/non-active comparison groups. The studies were generally of poor quality, with high heterogeneity, particularly with the number of sessions ranging from 2 to 96. Development and evaluation of a fatigue-specific social-psychological intervention is warranted in this setting.

ARTICLE HISTORY

Received 23 October 2016
Accepted 19 February 2017


KEYWORDS

End-stage kidney disease; haemodialysis; fatigue; psychosocial; intervention; meta-analysis; systematic review

Introduction

Chronic kidney disease (CKD) involves progressive renal damage and loss in renal functioning (Haynes & Winearls, 2010), leading to hypertension, an accumulation of calcium and phosphate, and impaired erythropoietin production (Haynes & Winearls, 2010; Levey et al., 2003; Levey et al., 2005; Levin et al., 2008). An estimated 8–16% worldwide suffer from CKD (Jha et al., 2013), with a 6–8% growth per annum of dialysis patients, classifying it as a worldwide epidemic (Levin, 2003). CKD management is complex, relying on treating the underlying causes, such as hypertension or diabetes, slowing down the progression of renal damage, treating CKD-related complications, like anaemia (Haynes & Winearls, 2010), and substituting the role of kidneys via renal replacement

CONTACT Federica Picariello  federica.picariello@kcl.ac.uk

 Supplemental data for this article can be accessed at [doi:10.1080/17437199.2017.1298045](https://doi.org/10.1080/17437199.2017.1298045).

© 2017 The Author(s). Published by Informa UK Limited, trading as Taylor & Francis Group
This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

therapy (RRT) in end-stage kidney disease (ESKD) (Haynes & Winearls, 2010; Levin et al., 2008). Renal insufficiency leads to a number of debilitating symptoms; fatigue, pruritus, sleep disturbance, pain, and dry skin were found to be the most prominent symptoms in advanced CKD (Almutary, Bonner, & Douglas, 2013; Murtagh et al., 2007).

Fatigue, a complex and subjective experience that has been described as 'extreme and persistent tiredness, weakness or exhaustion-mental, physical, or both' (Artom, Moss-Morris, Caskey, & Chilcot, 2014; David et al., 1990; Pawlikowska et al., 1994), has consistently emerged as a major affliction for CKD patients (Afshar, Rebollo-Mesa, Murphy, Murtagh, & Mamode, 2012; Caplin, Kumar, & Davenport, 2011; Curtin, Bultman, Thomas-Hawkins, Walters, & Schatell, 2002). It affects between 42% and 89% of ESKD patients, depending on treatment modality and fatigue measurement used (Artom et al., 2014; Bossola, Vulpio, & Tazza, 2011). There is extensive evidence that fatigue may lead to reduced functioning and poorer clinical outcomes (Artom et al., 2014; Bonner, Caltabiano, & Berlund, 2013; Bossola et al., 2015; Davison & Jhangri, 2010; Jhamb et al., 2009; Jhamb et al., 2011; Koyama et al., 2010); yet, it is often under-recognised and under-treated by healthcare professionals, and often normalised as part of the illness and treatment burden (Lee, Lin, Chaboyer, Chiang, & Hung, 2007; Weisbord et al., 2007). Fatigue-specific treatments are currently scarce, and the vast majority of existing treatments revolve around medications, such as L-carnitine, correction of anaemia, or involving patients in exercise. A review of pharmacological treatments for fatigue in CKD reached the conclusion that none of the drugs can be recommended for the prevention of fatigue, and complete and prolonged relief from fatigue is rare (Bossola et al., 2011). Whilst correction of anaemia has consistently shown great dose-response improvements in outcomes and quality of life, it is closely managed in renal patients, with Hb levels maintained between 10 and 12 g/dL in adults (Revicki et al., 1995). Consequently, there is a ceiling effect of anaemia management, and often fatigue persists when anaemia is controlled.

Exercise-based treatments are heterogeneous, varying in modality, delivery mode, frequency, duration, and intensity (Artom et al., 2014; Bossola et al., 2011). Multiple systematic reviews of exercise interventions in this patient population are currently available (Cheema & Singh, 2005; Heiwe & Jacobson, 2014; Segura-Ortí, 2010; Smart & Steele, 2011), and according to these, fatigue is rarely the primary treatment target, and any improvements in fatigue are extrapolated from quality of life outcomes. Therefore, exercise interventions may have some secondary benefits on the vitality levels of renal patients (Chang, Cheng, Lin, Gau, & Chao, 2010; Painter, Carlson, Carey, Paul, & Myll, 2000; Storer, Casaburi, Sawelson, & Kopple, 2005; van Bergen et al., 2009; van Vilsteren, de Greef, & Huisman, 2005). However, these exercise trials suffer from numerous methodological limitations including, small sample sizes, inadequate reporting of participants, intervention, and outcome characteristics, and low population validity, with the samples included in the majority of studies consisting of younger patients undergoing haemodialysis (Cheema & Singh, 2005; Heiwe & Jacobson, 2014; Segura-Ortí, 2010; Smart & Steele, 2011). Furthermore, exercise interventions have been repeatedly criticised for being unsuitable for patients with multi-morbidities, disabilities, and in poorer health (Kosmadakis et al., 2010). Whilst the effect of psychological interventions on fatigue in other chronic conditions have been more extensively studied (Cramp et al., 2013; Jacobsen, Donovan, Vadaparampil, & Small, 2007; Kangas, Bovbjerg, & Montgomery, 2008; Neill, Belan, & Ried, 2006; van den Akker et al., 2016), the number of studies examining fatigue-specific psychotherapies in this patient population is currently limited (Artom et al., 2014).

Rationale

Given the debilitating nature of fatigue in ESKD, its management represents a clinical priority (Artom et al., 2014). There is a need to systematically identify the currently available social-psychological interventions that have benefits on fatigue in the renal population and assess the extent of fatigue improvements across the different interventions. An estimate of the effectiveness in reducing fatigue of different interventions can also inform a future more comprehensive and fatigue-focused

intervention for renal patients. To the best of our knowledge, the efficacy of social-psychological interventions for the management of fatigue in ESKD has not been systematically reviewed to date.

Objectives

The objectives of our review are:

- (1) To assess the efficacy of current interventions at improving fatigue.
- (2) To identify whether differences in efficacy exist depending on behaviour change techniques (BCTs) used within the interventions.

Methods

Eligibility criteria

The inclusion/exclusion criteria can be found in Table 1. Only studies available in full-text were included to ensure sufficient appraisal and review. No publication date/status or language restrictions were imposed.

Table 1. PICOS inclusion/exclusion criteria.

	Inclusion criteria	Exclusion criteria
Study design	RCTs or quasi-RCTs: Studies were included if the authors used the word ‘random’ to describe the method for assigning subjects to groups.	Uncontrolled intervention studies, or case series studies, or observational studies.
Population	Adults (minimum age 18 years).	Children, adolescents (under 18 years).
Illness	CKD of any aetiology and duration, stages 3–5 (eGFR falling below 60 ml/minute/1.73m ²).	Primary stages of kidney disease when eGFR still normal or only slightly reduced (eGFR above 60 ml/minute/1.73 m ²).
Treatment	Haemodialysis, at home or at a satellite unit; peritoneal dialysis (automated or ambulatory); in pre-dialysis care, Tx.	Conservatively managed patients.
Intervention	A broad range of social-psychological interventions were included, either targeting fatigue or including fatigue/vitality as an outcome (primary or secondary). We defined social-psychological interventions according to criteria used in previous Cochrane reviews of social-psychological interventions for other long-term conditions (e.g., Goedendorp, Gielissen, Verhagen, & Bleijenberg, 2009; Poort et al., 2016). This definition included any intervention, involving systematic treatment with some form of feedback or review, including psychotherapy, psycho-education, and interventions containing elements like: education, goal-setting, cognitive restructuring, behavioural strategies, relaxation training, stress management, or support groups. Multimodal interventions, consisting of both psychological and other therapeutic strategies (e.g., exercise), were also included, if one or more social-psychological therapeutic technique was clearly evident. Both individual and group-focused interventions were included, regardless of delivery mode.	Excluding pharmacological interventions, exclusively exercise interventions, interventions modifying the dialysis schedule or parameters, alternative medicine interventions (e.g., acupuncture), interventions revolving around making specific changes to the diet, or psychological techniques aimed at improving adherence to exercise interventions.
Control	Any intervention versus placebo, no intervention (e.g., waiting-list control), or another active intervention (including interventions given alone or in combination).	N/A
Outcomes	A validated self-report measure of fatigue including VAS and the vitality subscale of the SF-36.	Excluding other outcomes, like physical functioning, sleep quality, quality of life, mortality or distress and muscle morphology outcomes, BMI, and objective laboratory measurements of aerobic capacity.

Note: RCT: randomised controlled trial; eGFR: estimated glomerular filtration rate; CKD: chronic kidney disease; Tx: kidney transplant recipient; VAS: visual analogue scale; BMI: body mass index.

Information sources

Studies were identified by searching the following databases: PsycInfo on Ovid (1806–Present), Medline on Ovid (1946–Present), Embase on Ovid (1974–Present), Global Health on Ovid (1973–Present), Web of Knowledge (Core Collection, KCI-Korean Journal Database, SCIELO), Cumulative Index to Nursing and Allied Health Literature (CINAHL) via EBSCOhost, and Cochrane Central Register of Controlled Trials (CENTRAL). Grey literature was also searched, through the following databases: (1) OpenGrey, (2) WorldCat, (3) British Library Electronic Theses Online Service (EThOS), and (4) DART-Europe E-theses portal, without any hits. Additionally, references of the eligible articles were screened to identify any relevant articles missed by the electronic and manual searches.

Search (December, 2015)

The search strategy included a combination of MeSH terms, and keywords with appropriate Boolean operators (online Appendix A). The quality of the search strategy, tailored for each database, was evaluated by a librarian with expertise in database searches for reviews and the strategies were revised accordingly. No limits were applied across the searches.

Study selection

The process of identifying studies for review consisted of four stages: identification, screening, eligibility, and inclusion (Moher, Liberati, Tetzlaff, Altman, & Group, 2010). During the identification stage, the chosen databases were searched and the citations were exported to EndNote X6. The citations were screened for duplicates and the eligibility criteria both through the help of EndNote X6 and a manual proof assessment that allowed the identification of papers reporting on the same dataset. The full-texts of the remaining citations were retrieved and assessed according to the inclusion/exclusion criteria, by two independent reviewers (FP and JLH) and any discrepancies were resolved by discussion and consensus. Where consensus could not be reached, feedback of a third author was sought. This process led to the final number of papers that were included in this review.

Data collection and extraction process

Data from the included studies were extracted using a data extraction form which was adapted from the data collection checklist by the Cochrane Effective Practice and Organisation of Care Review Group (EPOC) to suit the purpose of this review. Key aspects of data extraction included: participant characteristics, methods, fatigue outcome used, intervention description, data analyses, and results for fatigue as an outcome. Where missing data were encountered, authors were contacted to retrieve information. Descriptive data were presented using the Graphical Overview for Evidence Reviews software (GOfer; Stahl-Timmins, 2014). The reliability of the coding and data extraction was assessed by computing Kappa agreement between the two reviewers.

Outcome data

Recognised psychometric self-report measures of fatigue were extracted here, such as the Fatigue Severity Scale (FSS; Krupp, LaRocca, Muir-Nash, & Steinberg, 1989) or the Vitality subscale of the SF-36 (Ware Jr & Sherbourne, 1992; Ware, Snow, Kosinski, & Gandek, 1993).

To address Objective 2 and extrapolate BCTs of each intervention, the intervention descriptions were coded by two reviewers against the behaviour change taxonomy BCTs taxonomy (Michie et al., 2013) via the use of NVivo, a software developed for the analysis of qualitative data.

Quality and risk of bias assessments

Within-study bias

Risk of bias (RoB) was assessed by two reviewers using the Cochrane Risk of Bias assessment tool. The criteria used to assess RoB in this review included: random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and the identification of any other biases, such as inconsistent results, contamination between intervention and control groups, baseline non-equivalence between groups, and the possibility of conflict of interest judged from the funding information. Each study was classified into 'low', 'high', or 'unclear' RoB for each category. Disagreements were solved by discussion and consensus, in cases where consensus could not be reached, the opinion of a third reviewer was sought. Where information reported in the paper was insufficient or unclear, authors were contacted. RoB ratings were presented using RevMan5 (Cochrane Collaboration, 2014).

Additionally, all included studies underwent a quality assessment using a modified version of the Effective Public Health Practice Project (EPHPP) quality assessment tool for quantitative studies, with relevant considerations to suit the purposes of this review. The following categories were removed because they were captured by the RoB criteria: randomisation, differences between groups prior to the intervention, blinding, attrition, intervention integrity, and whether analysis were performed by intervention allocation status rather than the actual intervention received. Also, given that the RCT study design was an inclusion criterion, the study designs category was deemed redundant. Additional categories were added, pertaining to the analysis and report of the results.

Between-study bias

The risk of publication bias was evaluated to determine whether studies reporting statistically significant results were more likely to be published, potentially overestimating the real effect size (Rothstein, Sutton, & Borenstein, 2006). In order to assess whether this type of bias was likely here, a funnel plot for symmetry was constructed, displaying the effects size of the published studies against variance, with asymmetry suggesting the possibility of publication bias. However, funnel plots can be misleading and inaccurate, especially with few studies or if studies are heterogeneous (Walker, Hernandez, & Kattan, 2008). Because of the subjective nature of interpreting funnel plots the following objective tests were also used to support conclusions: the trim and fill method (Duval & Tweedie, 2000), a classic fail safe analysis, computing the number of studies needed to produce a null result (Rosenthal, 1979), Egger's test to measure funnel plot asymmetry (Egger, Smith, Schneider, & Minder, 1997; Sterne et al., 2011) and a comparison of the results between random-effects and fixed-effects models (Sterne et al., 2011).

Quality of intervention reporting

The intervention descriptions of all included studies were assessed using the Template for Intervention Description and Replication (TIDieR) checklist and guide (Hoffmann et al., 2014). TIDieR is intended as a tool for study authors and systematic reviewers to describe interventions accurately and consistently, with enough detail to allow replication. Two reviewers coded each intervention description against the checklist as being adequately reported, inadequately reported, not reported, or not applicable to the intervention. To provide a simple assessment of quality for each study, a value of 1 was assigned where the item was adequately described or not applicable, and a value of 0 where it was inadequately described or not reported (excluding Modifications and Tailoring items as 'Not reported' does not equate to a negative value, interventions that were not tailored or with no modifications received a score of 1).

Data analysis and synthesis

STATA's (Version 12 for Windows) *meta-eff* (Kontopantelis & Reeves, 2009) command was used to convert fatigue measures into standardised mean differences (SMDs) and standard errors. A DerSimonian–Laird (DerSimonian & Laird, 1986) random effects meta-analysis with 95% confidence intervals using STATA's *metan* (Harris et al., 2008) command was performed. A random effects model output was selected as it is more conservative than a fixed effects model and should be used when analysing real-world data (Field, 2003; Hunter & Schmidt, 2000). Forest plots were provided. Fatigue was recoded where necessary so low scores indicate greater fatigue. Where data were reported on multiple time points, effect sizes were computed for each time point. Across the studies, the earliest time point was favoured at follow-up.

The chi-squared statistic (Q) was used to test for the presence of heterogeneity across studies. The degree of statistical heterogeneity was estimated using the I^2 index, which describes the percentage of variation due to heterogeneity as opposed to by chance (Higgins & Thompson, 2002). Cochrane guidance provides cut-offs for interpretation of the magnitude of heterogeneity (Higgins et al., 2011).

A narrative synthesis was conducted following the guidance of Popay et al. (2006) to provide a textual summary of the findings across all the included studies. The GRADE approach (Schünemann, Brożek, & Oxman, 2013), a system for grading the quality of the evidence and providing a confidence judgement on how close the estimated effect is to the true effect, was also applied to the findings. In order to provide this judgement, the approach draws together information from the various quality assessments and analyses, such as how well the RoB criteria have been met, whether confounders have been accounted for, heterogeneity across the studies, the estimated effect's confidence intervals, and symmetry of the funnel plot.

Sensitivity and subgroup analyses

Sensitivity analysis were performed in order to detect whether the overall effect is affected by the inclusion of studies with imputed data and the quality of the evidence, specifically the RoB of each study for the allocation concealment category. This index quality criterion was selected because Pildal et al. (2007) showed that effect size estimates were inflated in studies with inappropriate allocation concealment. Additionally, the influence of each individual study on the overall meta-analysis estimate was also examined, using STATA's *metainf* command (Tobias, 1999).

Subgroup analyses were also conducted to assess if effect sizes vary according to the following characteristics (see online Appendix B for a coding manual), selected a priori: (1) country (Western vs. non-Western), (2) whether participants were fatigued at baseline, (3) fatigue as a primary or secondary outcome, (4) RRT modality (pre-dialysis care, haemodialysis, peritoneal dialysis, kidney transplantation), (5) intervention provided to control group, (6) level of training of intervention facilitator, (7) tailoring of the intervention, and (8) intervention components, more specifically: exercise, cognitive-behavioural therapy (CBT) techniques, and relaxation/stress management. Given the limited number of studies included in this review, formal meta-regression analyses could not be conducted. Sensitivity and subgroup analyses were conducted on the most complete dataset, using first time-point data of each study.

Results

Results of the search

The electronic and manual searches resulted in 5057 unique citations. Two review authors (FP and JLH) screened the titles and abstracts and identified 92 reports as potentially relevant, which were retrieved for further assessment. After full-text screening, 16 citations were deemed as eligible according to the inclusion and exclusion criteria (see Figure 1 for the PRISMA flow-chart diagram

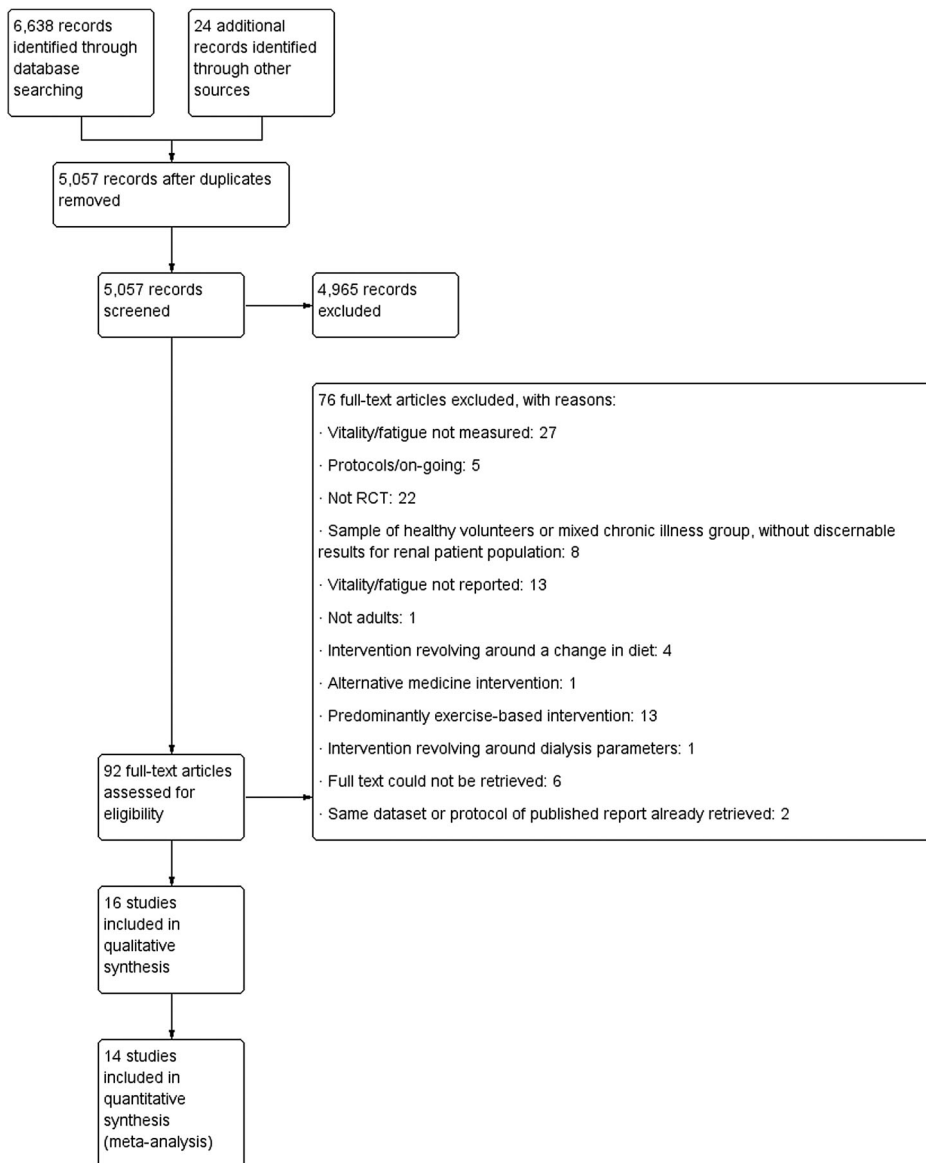


Figure 1. PRISMA flow-chart diagram. This figure shows the flow of the citations through the selection process. Titles and abstracts of 5057 records were screened. Out of these, 92 full-text articles were assessed for eligibility. Sixteen were deemed as eligible and 14 could be included in the meta-analysis. The most common reasons for exclusion after full-text appraisal were: (1) not measuring fatigue/vitality as an outcome, (2) failing to report discernable fatigue/vitality findings, and (3) not a randomised or quasirandomised controlled study design.

and online Appendix C for the inclusion/exclusion criteria screening table). The included studies are displayed in [Figure 2](#), from here onwards studies will be referred to by using their reference number displayed in [Figure 2](#). Citations of the included studies can be found in online Appendix D. A summary of the study characteristics and demographics are presented in [Figure 2](#). Out of the 16 trials, 14 randomised participants at the individual level, 2 were cluster trials, where dialysis shifts were randomised rather than participants (7, 12). Six potentially eligible ongoing/not yet published trials were identified and these will be considered in future updates of this review (online Appendix E).

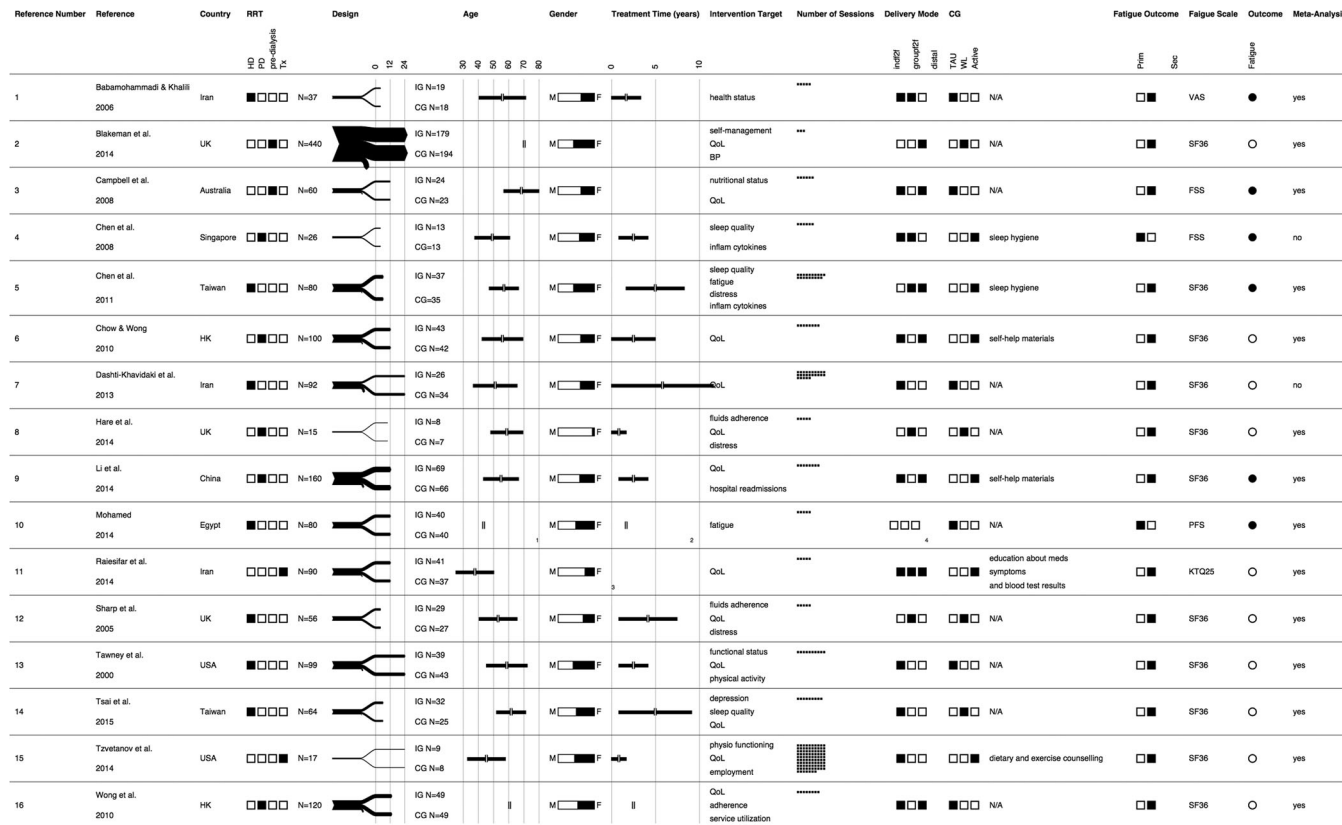


Figure 2. Graphical representation of the characteristics of the included studies. This figure summarises the main descriptive characteristics of the included studies. ^{1,2} estimated from frequencies; ³ not reported; ⁴ unclear; CG: control group; IG: intervention group; M: male; F: female; QoL: quality of life; indf2f: individual face-to-face; groupf2f: group face-to-face; TAU: treatment as usual; WL: waiting-list control; Prim: primary outcome; Sec: secondary outcome; VAS: visual analogue scale; SF36: vitality subscale of the SF-36; FSS: fatigue severity scale; PFS: Piper fatigue scale; KTQ25: fatigue subscale of the kidney transplant questionnaire.

Characteristics of the included studies

Sixteen trials were included with a total of 1536 randomised participants. Trial sample sizes ranged from 15 to 440 participants. The trials were conducted in 9 different countries: UK (2, 8, 12), USA (13, 15), Australia (3), Hong Kong (6, 16), Singapore (4), Taiwan (5, 14), China (9), Iran (1, 7, 11), and Egypt (10).

With regards to demographic characteristics of the samples, there was a fairly equal distribution of males (51.5%) and females across the studies. Samples of all the included studies consisted of adults, with a weighted mean age of 60.5. For the studies including dialysis patients, the mean weighted length on dialysis was 3.78 years. Studies did not specify what proportion of participants were in receipt of anaemia treatments. A total of 86 participants reported long-term use of hypnotics in three studies (4, 5, 14).

Fatigue was a primary outcome in two studies (4, 10), but only the intervention in study 10 was designed specifically for fatigue. In the rest of the studies, fatigue was a secondary outcome, generally as part of a broader quality of life assessment (2–3, 6–9, 11–16). Eleven studies used the vitality subscale of the SF-36 as a measure of fatigue, with only three studies relying on a validated fatigue-specific instrument (4, 5, 10). Six studies (6, 8, 9, 10, 11, 16) assessed outcomes on multiple occasions after the intervention, while the remaining studies used a single assessment. Ten studies assessed outcomes shortly after the intervention (less than 6 weeks; 1, 4, 5, 6, 8, 9, 10, 11, 12, 14), while 11 assessed outcomes at longer intervals following the intervention (more than 6 weeks; 2, 3, 6, 7, 8, 9, 10, 11, 13, 15, 16). Out of the 16 studies, only 6 found a significant improvement in fatigue following the delivered intervention (1, 3–5, 9, 10), 5 of these were carried out among dialysis patients, and only one was aimed at patients in pre-dialysis care. Two trials could not be included in the meta-analysis because of the non-normal distribution of their data (4, 7).

Meta-analysis

According to the most complete dataset, relying on the first time-point data of each trial, there was a small to medium significant effect of social-psychological interventions on fatigue across the 14 RCTs ($N = 1232$; $SMD = 0.37$, $p = .001$; 95% confidence interval [CI] 0.15 to 0.59, $I^2 = 69.1\%$, $p < .001$; See [Figure 3](#)). Social-psychological interventions were associated with a significant improvement in fatigue. The findings were comparable when examining short-term follow-up data (up to 6 weeks) and long-term follow-up (more than 6 weeks) (online Appendix F). Heterogeneity was greatest for follow-up data. Follow-up time points ranged from 2 weeks to 6 months.

Sensitivity analyses

Impact of imputed data and influence of individual studies

Sensitivity analyses were conducted to repeat the primary meta-analytic computations where arbitrary decisions were made due to missing information or lack of clarity in the reports. Due to missing values, data were imputed for two studies (8, 15). More specifically, in study 8, baseline standard deviations were used at follow-up, while in study 15, vitality values were estimated from a bar chart. Sensitivity analyses were conducted on the most complete dataset of first time points excluding these two studies, to assess the impact of imputed data on the meta-analytic findings. This resulted in a smaller SMD of 0.28 and reduced heterogeneity ($p = .004$; 95% CI 0.09 to 0.47, $I^2 = 58.9\%$, $p = .005$; see online Appendix G). Online Appendix H shows graphically the influence of omitting one study in each turn on the overall meta-analysis estimate, with mainly little effect on the overall meta-analysis estimate and 95% CI.

Quality of the included studies

Studies were rated for quality across the following domains: focus of research question, sample representativeness, sampling method, response rate, power calculation, acknowledgement of confounders,

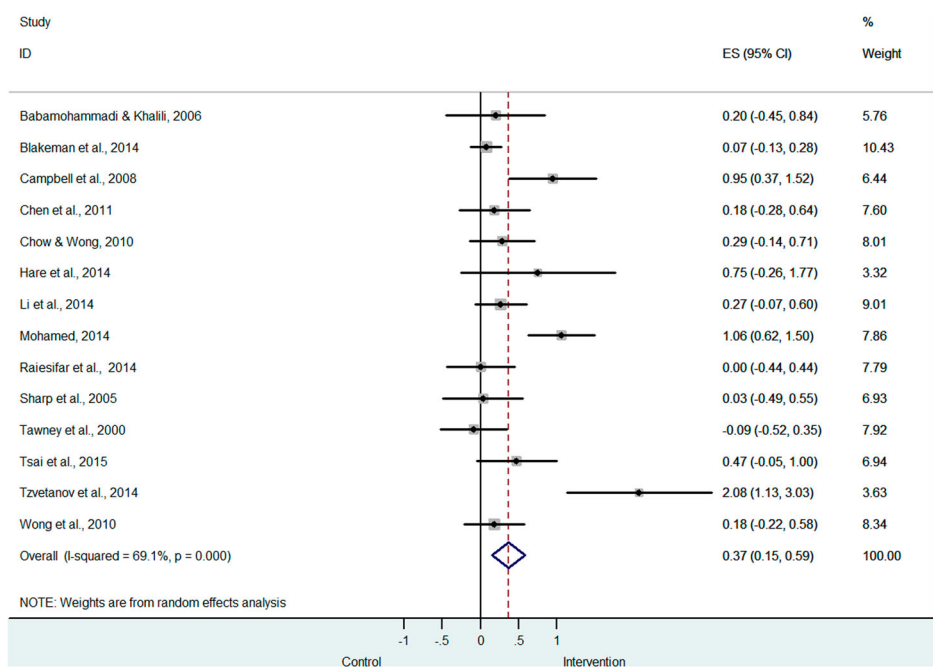


Figure 3. Forest plot of the effect of social-psychological interventions on fatigue using first time-point data. This diagram is a graphical representation of the meta-analytic findings, showing the earliest time-point effect sizes and errors of each included study. There was a significant effect of social-psychological interventions on fatigue, in favour of the intervention.

validity and reliability of the instruments used, appropriateness of the statistical analyses, report of significance levels and confidence intervals, and adjustment of the p -value for multiple analyses. Almost all studies addressed clearly focused questions, provided clear inclusion/exclusion criteria, relied on recognised self-report instruments, and assessed and reported statistical significance. Power calculations were reported in 10 studies, and 9 studies reported a response rate of 70% or over. Poor methodological quality was evident in relation to sample representativeness. Largely studies relied on single-centre opportunistic recruitment with little attention devoted to confounders and p -value adjustment for multiple analyses. Confidence intervals were mostly not reported. Please see online Appendix I for the full-quality assessment of each study. Inter-rater agreement for the quality assessment was generally substantial, ranging from $\kappa = 0.242$ to $\kappa = 1.00$. Agreement was lower with regards to the representativeness of the sample ($\kappa = 0.242$) and appropriateness of the statistical methods ($\kappa = 0.360$).

With regards to the intervention reporting, the average TiDiER rating across the studies was of 7.5, suggesting that an adequately described judgement was only granted for around half of the TiDiER categories (see online Appendix J for a further breakdown for each category). The categories most often well reported were: Brief Name, Rationale, and Tailoring. Although generally rationales were provided in the reports, predominantly the interventions were not theory-led, with only a minority of studies providing adequate detail on any theoretical underpinnings (2, 8, 12, 16). Consistently, reporting was poor of the Materials and Fidelity categories (planned and actual). Inter-rater agreement for the TiDiER assessment ranged from $\kappa = 0.259$ to $\kappa = 0.862$.

RoB of the included studies

Due to inadequate reporting across the included studies, it was often not possible to determine whether a quality or RoB criterion was met. As can be seen from Figure 4 and online Appendix K, the studies were predominantly of poor quality with a strong prevalence of unclear or high RoB

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Babamohammadi & Khalili, 2006	?	?	?	?	?	?	-
Blakeman et al., 2014	+	+	-	-	+	+	+
Campbell et al., 2008	+	+	?	?	-	+	?
Chen et al., 2008	+	+	?	?	+	-	+
Chen et al., 2011	+	+	-	?	+	?	?
Chow & Wong, 2010	+	?	?	?	-	?	-
Dashti-Khavidaki et al., 2013	-	-	-	-	-	?	-
Hare et al., 2014	+	-	-	-	+	?	-
Li et al., 2014	+	?	?	?	-	?	-
Mohamed, 2014	?	?	?	?	+	?	-
Raiesifar et al., 2014	?	?	?	?	-	?	-
Sharp et al., 2005	+	+	-	-	+	?	-
Tawney et al., 2000	?	?	?	?	-	?	-
Tsai et al., 2015	+	+	-	+	-	?	-
Tzvetanov et al., 2014	+	+	?	?	?	?	-
Wong et al., 2010	+	+	+	+	-	?	+

Figure 4. RoB summary: review authors' judgements about each RoB item for each included study. This diagram is a graphical summary of the judgements for each RoB category each included study received.

judgements, particularly for the categories of incomplete outcome data, selective reporting, blinding, and other biases, such as poor description of the control condition and likelihood of contamination between the trial arms. Inter-rater agreement for the RoB assessment was high, ranging from $\kappa = 0.462$ (for the category Blinding of Personnel) to $\kappa = 0.830$ (for the category Selective Reporting).

Impact of RoB: allocation concealment

Of those studies meta-analysed, seven studies were rated as low RoB for allocation concealment. To assess the impact of high or unclear RoB for allocation concealment, the estimated SMD of studies with high or unclear RoB were compared against those with low RoB for allocation concealment (see online Appendix L, *Figure L.1*). This analysis revealed an increased effect of social-psychological interventions with adequate allocation concealment on fatigue (SMD = 0.43, $p = .014$; 95% CI 0.09 to 0.77, $I^2 = 74.9\%$, $p = .001$). This analysis was rerun, excluding study 15, due to its outlying nature. Once removed the effect size of social-psychological interventions was reduced to SMD = 0.25 ($p = .031$; 95% CI 0.02 to 0.48; $I^2 = 44.7\%$, $p = .108$; $N = 6$; see online Appendix L, *Figure L.2*).

Interventions

Great variability was evident in relation to intervention content and structure. Frequency and duration of treatment sessions varied considerably among the trials, with a minimum number of 2 sessions (2) and up to 96 sessions (15), with a median of 6 sessions. The majority of interventions were delivered face-to-face, individually and/or in a group format. Some interventions provided an initial face-to-face assessment, and subsequently over the phone sessions (3, 6, 9, 16). Across the interventions, most sessions lasted between 30 and 60 minutes (4–6, 8, 10, 12–15). All interventions included some form of education. The only intervention designed specifically to target fatigue was an educational intervention (10). Five interventions were CBT-based, two targeting sleep quality (4, 5), two were aimed at improving adherence to fluid restrictions (8, 12), and one targeting physical functioning (15). The latter also included a physical component, consisting of resistance training (15). Four interventions revolved around shared-care and the role of practical support from nurses to improve quality of life (1, 6, 11, 16). In study 2, peer-led support to facilitate access to community support was offered in order to improve self-management and quality of life. The intervention in study 3 was a nutrition intervention, revolving around self-management of diet restrictions, in order to improve nutritional status. Study 7's intervention was a pharmaceutical care programme aimed at improving quality of life. The intervention in study 13 was an educational and behavioural intervention, to increase active participation in daily activities, aimed at improving functional status. Lastly, one intervention was a nurse-led breathing relaxation programme targeting depression (14).

When studies were coded according to BCTs, the following intervention categories were prevalent. The majority of interventions involved goal-setting and/or problem-solving (1–3, 6–9, 11–13, 15, 16). Another prevalent category of BCTs used in the interventions was social support. Techniques from the category of Repetition and Substitution and advice on how to avoid cues for the unwanted behaviour were provided within CBT-based interventions (4, 5, 8, 12). Stress-management and relaxation techniques were used in a minority of interventions (4, 5, 8, 10, 12, 14, 15). Graded tasks were explicitly only used by one study, to facilitate an increase in self-efficacy around physical activity (13) and only one study included the use of cues to facilitate performance of physical activity in patients (13). A minority of interventions also included exercise/physical activity components, alongside social-psychological strategies (10, 13, 15). For a full summary of the techniques used in each intervention see online Appendix M.

In relation to the comparison group, most studies compared the intervention to a treatment as usual (1, 3, 7, 10, 13, 16) or waiting-list control (2, 8, 12, 14), with only six studies using an active or enhanced comparison group (4–6, 9, 11, 15).

Exploratory subgroup (moderator) analyses

Exploratory subgroup analyses were conducted to identify potential moderators of the pooled effect size of social-psychological interventions on fatigue. The variables used in these analyses were selected a priori. There was an insufficient number of studies in subcategories of exercise ($N = 3$),

fatigue as a primary outcome ($N = 1$), non-tailored interventions ($N = 2$), and interventions targeted at kidney transplant recipients ($N = 3$) or patients in pre-dialysis care ($N = 2$); therefore, the influence of these factors on the effectiveness of social-psychological interventions on fatigue could not be determined. The pooled effect size did not seem to vary by country where the study was conducted (online Appendix N).

Even though pooled effect sizes were similar between studies with fatigued samples versus those that were deemed non-fatigued ($SMD = 0.37$ vs. $SMD = 0.43$, respectively); the pooled effect size became non-significant for the latter category (online Appendix N). Furthermore, a more conservative cut-off for vitality (cut-off ≤ 45) resulted in a more pronounced difference in favour of fatigued samples (online Appendix N).

Similarly, effect sizes were comparable between passive and active/enhanced comparison groups ($SMD = 0.36$ vs. $SMD = 0.40$, respectively). However, the pooled effect size of interventions compared to an active comparison group became non-significant (online Appendix N).

Surprisingly, when examining the influence of the level of training of the intervention facilitator, the effect size was smaller for studies with intervention facilitators who received extensive training and had experience in delivering the intervention ($SMD = 0.16$, $p = .027$; 95% CI 0.02 to 0.30, $I^2 = 0\%$, $p = .677$) compared to facilitators who received lower levels of training ($SMD = 0.56$, $p = .013$; 95% CI 0.12 to 1.00, $I^2 = 81.9\%$, $p < .0001$).

When comparing CBT-based interventions with interventions not relying on CBT techniques, the estimated effect size of CBT-based interventions was larger, but albeit non-significant ($SMD = 0.67$, $p = .086$; 95% CI -0.10 to 1.44 , $I^2 = 80.3\%$, $p = .002$) compared to the other interventions ($SMD = 0.31$, $p = .005$; 95% CI 0.09 to 0.54, $I^2 = 65.6\%$, $p = .002$) (online Appendix N).

The greatest variation in effect emerged between studies including stress-management/relaxation techniques and those without such techniques. The SMD was greater among interventions including stress-management/relaxation techniques ($SMD = 0.69$, $p = .007$; 95% CI 0.19 to 1.19, $I^2 = 76.7\%$, $p = .001$) compared to interventions without these techniques ($SMD = 0.19$, $p = .032$; 95% CI 0.02 to 0.36, $I^2 = 33.2\%$, $p = .163$) (online Appendix N).

RoB across studies

The somewhat asymmetrical funnel plot, due to the absence of studies in the lower left corner (Figure 5), and significant Egger's statistical test (bias = 2.51; 95% CI 0.15 to 4.88; $p = .039$) across all the included studies indicate that the review may be subject to publication bias. When the risk of publication bias analysis was recomputed excluding studies with imputed data (8, 15), small study publication bias disappeared, demonstrated by a more symmetrical funnel plot (online Appendix O) and a non-significant Egger's statistical test (bias = 1.75; 95% CI -1.21 to 4.70 ; $p = .216$).

According to the trim and fill method, an additional four imputed studies would reduce the pooled effect size to 0.150 (95% CI -0.11 to 0.41), yielding a non-significant effect of social-psychological interventions on fatigue ($p = .259$; see online Appendix P). However, this finding should be interpreted with caution as this method is unreliable in the presence of substantial between-study heterogeneity (Peters, Sutton, Jones, Abrams, & Rushton, 2007; Terrin, Schmid, Lau, & Olkin, 2003), as has been observed here. To further assess small study bias, a fixed effects model was computed and the values were compared to a random effects model output. The two models were comparable (random-effects: $SMD = 0.37$, $p = .001$; 95% CI 0.15 to 0.59, $I^2 = 69.1\%$, $p < .001$ vs. fixed-effects: $SMD = 0.26$, $p < .0001$; 95% CI 0.15 to 0.37), suggesting only small bias, without considerable influence on the estimated efficacy of interventions on fatigue. Finally, a classic fail safe analysis was computed, suggesting that in order to produce a null-effect of social-psychological interventions on fatigue an additional 129 null-effect studies would be needed (overall Z score = 19.66).

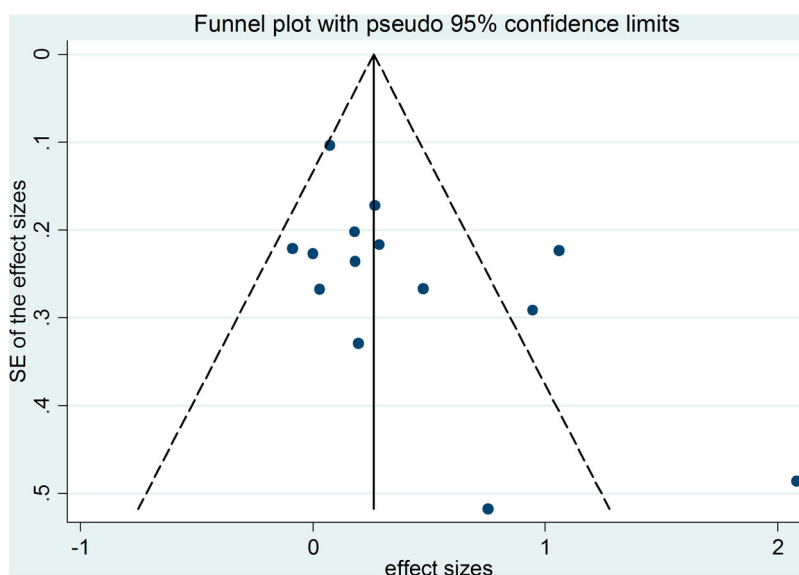


Figure 5. Funnel plot to assess publication bias. A scatterplot of treatment effect against a measure of study precision, to visually inspect the studies for publication bias and systematic heterogeneity.

GRADE appraisal of the findings

Using the GRADE methodology of appraisal of the quality of the evidence (Schünemann et al., 2013), the true effect identified by the meta-analysis here is likely to be substantially different from the true effect of social-psychological interventions on fatigue. This is because of the low methodological quality, high RoB across many of the categories, indirectness and imprecision of the data, and possibility of publication bias. Please see online Appendix Q for further information on the rating for each GRADE category.

Discussion

Summary of the findings

The aim of this review was to identify currently available social-psychological interventions for the management of fatigue in ESKD and to evaluate their efficacy. Sixteen social-psychological interventions were identified, in which the effect on fatigue was tested in an RCT. Although the results of 10 trials failed to find a significant improvement in fatigue following the delivery of a social-psychological intervention, the quantitative synthesis demonstrated significant small to moderate improvements in fatigue following social-psychological interventions, across follow up time-points ($N = 14$; $SMD = 0.37$, $p = .001$; 95% CI 0.15–0.59, $I^2 = 69.1\%$, $p < .001$). Except for one trial, none of the interventions were designed specifically to treat fatigue, and findings in relation to energy levels as an outcome were mostly extrapolated from the SF-36 vitality subscale. The majority of interventions were aimed at improving quality of life. The CBT-based interventions were either targeting sleep quality, or adherence to fluid restrictions, or physical functioning. There was some evidence to suggest greater effectiveness of interventions including stress-management and relaxation techniques for the reduction of fatigue compared to interventions without such techniques and tested among fatigued patients. The standardised pooled effect size became non-significant for trials with non-fatigued samples and when interventions were compared to active/enhanced comparison groups. There was no apparent benefit of CBT-based interventions versus interventions without CBT techniques.

Overall the identified studies were very different in terms of patient characteristics and intervention content and structure. In general, the quality of the studies appeared low, with many studies failing to control for confounders, relying on poor statistical methods, and lacking confidence intervals.

With regards to RoB, there was a strong prevalence of unclear or high RoB judgements especially evident for the categories of allocation concealment and incomplete outcome data. Many studies also provided poor descriptions of the comparison group. It is likely, as suggested by Pildal et al. (2007), that inclusion of studies with high or unclear RoB for allocation concealment may overinflate the SMD, as has been observed here. Additionally, there was indication for some publication bias. However, given that fatigue was mainly not the primary outcome, this may be attenuated and just a reflection of the gap in the literature.

Given the numerous methodological limitations, possibility of publication bias, and high heterogeneity from study to study, as it reached and even surpassed 50% (Higgins & Thompson, 2002), the findings should be interpreted with caution. High heterogeneity was particularly evident in the analyses of longer term follow-ups, this may stem from considerable variation in lengths of follow-up, ranging from 2 weeks to 6 months, alongside sample size differences, and differences in RRT and interventions, with the number of sessions ranging from 2 to 96. Additionally, poor methodological quality may result in an underestimated effect size of social-psychological interventions, as has been observed in another systematic review, where trials that relied on appropriate statistical methods, including use of intention-to-treat, reported a significantly greater effect size compared to exercise interventions (Kangas et al., 2008). Overall, according to the GRADE approach, the true effect of social-psychological interventions on renal fatigue is likely to be substantially different from the effect estimated here.

Previous research

There is increasing recognition regarding the importance of psychological factors in the perpetuation and maintenance of fatigue symptoms in chronic conditions (Donovan, Small, Andrykowski, Munster, & Jacobsen, 2007; Irving, Matcham, Ali, & Chalder, 2015; van Kessel & Moss-Morris, 2006). A greater appreciation for the role of these factors in fatigue has translated into successful psychological interventions, leading to clinically significant improvements in fatigue symptoms and fatigue-related functional impairment in cancer and Multiple Sclerosis (MS) (Gielissen, Verhagen, Witjes, & Bleijenberg, 2006; van Kessel et al., 2008). A number of systematic reviews are available across chronic conditions documenting the effectiveness of a range of social-psychological interventions for fatigue, with small to moderate effect sizes according to Cohen's classification (Cramp et al., 2013; Jacobsen et al., 2007; Kangas et al., 2008; Neill et al., 2006; van den Akker et al., 2016).

Although, in one study, both CBT designed specifically to treat social-psychological factors maintaining fatigue and relaxation training (RT) showed significant improvements in MS fatigue, the reduction in fatigue was greater in the CBT group over time compared to the RT group, as well as CBT yielding improvements in depression and anxiety (van Kessel et al., 2008). This was not observed here, the estimated effect size of CBT-based interventions was larger, but not significant compared to the other interventions without CBT techniques. A possible explanation for this finding is that as interventions were not designed specifically to improve fatigue, fatigue-specific beliefs, and behaviours were not addressed in treatment. In fact, studies that have evaluated the mechanisms of change following CBT corroborate the mediating role fatigue beliefs play in treatment effectiveness (Chalder, Goldsmith, White, Sharpe, & Pickles, 2015; Knoop, Van Kessel, & Moss-Morris, 2012; Wiborg, Knoop, Prins, & Bleijenberg, 2011). In fact, according to Knoop et al. (2012)'s analyses, the reduction in fatigue following CBT was unrelated to improvements in depression, emphasising the importance of specific fatigue-related beliefs being targeted within the intervention rather than general negative self-evaluations that are characteristic of depression. Any secondary benefits of non-fatigue-specific CBT interventions on energy levels may be the result of addressing more general beliefs about the

illness and other symptoms during treatment (Skerrett & Moss-Morris, 2006; van der Werf, Evers, Jongen, & Bleijenberg, 2003) or the benefits of improved mood on fatigue (Knoop et al., 2012; Stepanski et al., 2009).

Similar to the findings here, the primary aim of most social-psychological interventions, among cancer and rheumatoid arthritis patients, is rarely fatigue reduction and there is often no apparent consideration of fatigue mechanisms (Cramp et al., 2013; Kangas et al., 2008). As a consequence, levels of fatigue are consistently not specified as an inclusion criterion, possibly leading to samples without clinically significant severe fatigue and therefore resulting in a ceiling effect (Cramp et al., 2013; Kangas et al., 2008). In fact, the fatigue effect size estimated here became non-significant in samples that were deemed non-fatigued compared to fatigued ones. The importance of fatigue being the target of treatment within social-psychological treatment models has been accentuated by a systematic review of non-pharmacological fatigue interventions in cancer, where moderation analyses revealed the superiority of social-psychological interventions aimed at fatigue (including a fatigue aim or hypothesis) compared to exercise interventions aimed at fatigue; whereas the opposite was true across non-fatigue-specific interventions (Kangas et al., 2008). This indicates that the effect size of social-psychological interventions found here may be underestimated due to the lack of fatigue-specific focus among the included studies.

Potential biases in the review process

Our study identification and data extraction procedures adhered to Cochrane's robust methodological procedures and involved more than one researcher at each stage, thus allowing greater confidence in the validity and reliability of our review findings. As per Cochrane guidelines, the effect of methodologically strong and weak studies was explored throughout the meta-analytic work.

The main weakness of the current review was the intentionally broad inclusion criteria that resulted in high heterogeneity between the included studies. The definition of a social-psychological intervention was wide-ranging and renal patients undergoing different types of RRT or in pre-dialysis care were included. This was done to ensure the inclusion of all social-psychological interventions that may have potential to reduce renal fatigue. Poor Kappa agreements were evident for some more subjective and less quantifiable categories of the TIDieR and EPHPP assessments. Additionally, because the number of studies included in this review was relatively small, it was statistically inappropriate to perform formal moderation analyses.

Implications for research and practice

Social-psychological interventions may help to reduce fatigue in ESKD; however, there is currently a gap in theory-driven social-psychological interventions aimed at fatigue and evaluated in methodologically rigorous trials. There is extensive evidence in support of CBT for the treatment of fatigue, including techniques like goal-setting, graded tasks, and pacing aimed at fatigue (Kangas et al., 2008; van den Akker et al., 2016; White et al., 2011). However, there is need for a clear framework that elaborates on what fatigue beliefs and behaviours should be the target of treatment. Future interventions need to focus specifically on fatigue and be conducted with fatigued samples. This review highlighted an over-reliance on the vitality subscale as a marker of fatigue, although relatively consistent across studies this simplifies pooling of data, the consistent use of a fatigue-specific instrument validated in ESKD would increase the trustworthiness of the findings. Additionally, medications used for the management of anaemia need to be accounted for when looking at fatigue as an outcome. Further to this, it is essential that trials are reported in line with the CONSORT statement.

Conclusion

In conclusion, this meta-analytic review supports the efficacy of social-psychological interventions for the management of fatigue in ESKD. However; there was high variability across the studies, poor methodological quality, and possibility of publication bias which undermine the findings reported here. Given the successful application of social-psychological interventions for the management of fatigue in other chronic conditions and the additional burden fatigue poses on renal patients; development and evaluation of a fatigue-specific social-psychological intervention is warranted in this patient population. It is important that any fatigue intervention is tested in participants who are fatigued, to ensure that the potential efficacy is not merely masked by a ceiling effect.

Acknowledgements

The authors wish to thank Dr Sam Norton for his statistical expertise, Ms Karen Poole for her helpful feedback on the search strategies, and Diane Joung and Ellie Semsar for help with screening articles. PROSPERO registration number: CRD42016037123.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

This work was funded by a Biomedical Research Studentship to Miss Federica Picariello from the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

References

- Afshar, M., Rebollo-Mesa, I., Murphy, E., Murtagh, F. E., & Mamode, N. (2012). Symptom burden and associated factors in renal transplant patients in the UK. *Journal of Pain and Symptom Management*, 44(2), 229–238.
- van den Akker, L. E., Beckerman, H., Collette, E. H., Eijssen, I. C. J. M., Dekker, J., & de Groot, V. (2016). Effectiveness of cognitive behavioral therapy for the treatment of fatigue in patients with multiple sclerosis: A systematic review and meta-analysis. *Journal of Psychosomatic Research*, 90, 33–42.
- Almutary, H., Bonner, A., & Douglas, C. (2013). Symptom burden in chronic kidney disease: A review of recent literature. *Journal of Renal Care*, 39(3), 140–150.
- Artom, M., Moss-Morris, R., Caskey, F., & Chilcot, J. (2014). Fatigue in advanced kidney disease. *Kidney International*, 86(3), 497–505.
- van Bergen, M., Takken, T., Engelbert, R., Groothoff, J., Nauta, J., van Hoeck, K., ... Lilien, M. (2009). Exercise training in pediatric patients with end-stage renal disease. *Pediatric Nephrology*, 24(3), 619–622.
- Bonner, A., Caltabiano, M., & Berlund, L. (2013). Quality of life, fatigue, and activity in Australians with chronic kidney disease: A longitudinal study. *Nursing & Health Sciences*, 15(3), 360–367.
- Bossola, M., Di Stasio, E., Antocicco, M., Panico, L., Pepe, G., & Tazza, L. (2015). Fatigue is associated with increased risk of mortality in patients on chronic hemodialysis. *Nephron*, 130(2), 113–118.
- Bossola, M., Vulpio, C., & Tazza, L. (2011). Fatigue in chronic dialysis patients. *Seminars in Dialysis*, 24(5), 550–555.
- Caplin, B., Kumar, S., & Davenport, A. (2011). Patients' perspective of haemodialysis-associated symptoms. *Nephrology Dialysis Transplantation*, 26(8), 2656–2663.
- Chalder, T., Goldsmith, K. A., White, P. D., Sharpe, M., & Pickles, A. R. (2015). Rehabilitative therapies for chronic fatigue syndrome: A secondary mediation analysis of the PACE trial. *The Lancet Psychiatry*, 2(2), 141–152.
- Chang, Y., Cheng, S.-Y., Lin, M., Gau, F.-Y., & Chao, Y.-F. C. (2010). The effectiveness of intradialytic leg ergometry exercise for improving sedentary life style and fatigue among patients with chronic kidney disease: A randomized clinical trial. *International Journal of Nursing Studies*, 47(11), 1383–1388.
- Cheema, B. S. B., & Singh, F. (2005). Exercise training in patients receiving maintenance hemodialysis: A systematic review of clinical trials. *American Journal of Nephrology*, 25(4), 352–364.
- Cochrane Collaboration. (2014). Review Manager (RevMan) [Computer program] Version 5.2. 3. Copenhagen: The Nordic Cochrane Centre; 2012.

- Cramp, F., Hewlett, S., Almeida, C., Kirwan, J. R., Choy, E. H., Chalder, T., ... Christensen, R. (2013). Non-pharmacological interventions for fatigue in rheumatoid arthritis. *Cochrane Database Systematic Reviews*, 8, 1–75.
- Curtin, R. B., Bultman, D. C., Thomas-Hawkins, C., Walters, B. A., & Schatell, D. (2002). Hemodialysis patients' symptom experiences: Effects on physical and mental functioning. *Nephrology Nursing Journal*, 29(6), 562–574.
- David, A., Pelosi, A., McDonald, E., Stephens, D., Ledger, D., Rathbone, R., & Mann, A. (1990). Tired, weak, or in need of rest: Fatigue among general practice attenders. *BMJ*, 301(6762), 1199–1202.
- Davison, S. N., & Jhangri, G. S. (2010). Impact of pain and symptom burden on the health-related quality of life of hemodialysis patients. *Journal of Pain and Symptom Management*, 39(3), 477–485.
- DerSimonian, R., & Laird, N. (1986). Meta-analysis in clinical trials. *Controlled Clinical Trials*, 7(3), 177–188.
- Donovan, K. A., Small, B. J., Andrykowski, M. A., Munster, P., & Jacobsen, P. B. (2007). Utility of a cognitive-behavioral model to predict fatigue following breast cancer treatment. *Health Psychology*, 26(4), 464–472.
- Duval, S., & Tweedie, R. (2000). Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics*, 56(2), 455–463.
- Egger, M., Smith, G. D., Schneider, M., & Minder, C. (1997). Bias in meta-analysis detected by a simple, graphical test. *BMJ*, 315(7109), 629–634.
- Field, A. P. (2003). The problems in using fixed-effects models of meta-analysis on real-world data. *Understanding Statistics: Statistical Issues in Psychology, Education, and the Social Sciences*, 2(2), 105–124.
- Gielissen, M. F., Verhagen, S., Witjes, F., & Bleijenberg, G. (2006). Effects of cognitive behavior therapy in severely fatigued disease-free cancer patients compared with patients waiting for cognitive behavior therapy: A randomized controlled trial. *Journal of Clinical Oncology*, 24(30), 4882–4887.
- Goedendorp, M. M., Gielissen, M., Verhagen, C. A., & Bleijenberg, G. (2009). Social-psychological interventions for reducing fatigue during cancer treatment in adults. *Cochrane Database Systematic Reviews*, 1, 1–65.
- Harris, R., Bradburn, M., Deeks, J., Harbord, R., Altman, D., & Sterne, J. (2008). Metan: Fixed-and random-effects meta-analysis. *Stata Journal*, 8(1), 3–28.
- Haynes, R. J., & Winearls, C. G. (2010). Chronic kidney disease. *Surgery (Oxford)*, 28(11), 525–529.
- Heiwe, S., & Jacobson, S. H. (2014). Exercise training in adults with CKD: A systematic review and meta-analysis. *American Journal of Kidney Diseases*, 64(3), 383–393.
- Higgins, J. P., Altman, D. G., Gøtzsche, P. C., Jüni, P., Moher, D., Oxman, A. D., ... Sterne, J. A. (2011). The Cochrane collaboration's tool for assessing risk of bias in randomised trials. *BMJ*, 343, d5928–d5928.
- Higgins, J. P., & Thompson, S. G. (2002). Quantifying heterogeneity in a meta-analysis. *Statistics in Medicine*, 21(11), 1539–1558.
- Hoffmann, T. C., Glasziou, P. P., Boutron, I., Milne, R., Perera, R., Moher, D., ... Johnston, M. (2014). Better reporting of interventions: Template for intervention description and replication (TIDieR) checklist and guide. *BMJ*, 348, g1687–g1687.
- Hunter, J. E., & Schmidt, F. L. (2000). Fixed effects vs. random effects meta-analysis models: Implications for cumulative research knowledge. *International Journal of Selection and Assessment*, 8(4), 275–292.
- Irving, K., Matcham, F., Ali, S., & Chalder, T. (2015). 085. Fatigue and functional disability in rheumatoid arthritis: Evidence for a cognitive behavioural model. *Rheumatology*, 54(suppl 1), i83–i84.
- Jacobsen, P. B., Donovan, K. A., Vadaparampil, S. T., & Small, B. J. (2007). Systematic review and meta-analysis of psychological and activity-based interventions for cancer-related fatigue. *Health Psychology*, 26(6), 660–667.
- Jha, V., Garcia-Garcia, G., Iseki, K., Li, Z., Naicker, S., Plattner, B., ... Yang, C.-W. (2013). Chronic kidney disease: Global dimension and perspectives. *The Lancet*, 382(9888), 260–272.
- Jhamb, M., Argyropoulos, C., Steel, J. L., Plantinga, L., Wu, A. W., Fink, N. E., ... Unruh, M. L. (2009). Correlates and outcomes of fatigue among incident dialysis patients. *Clinical Journal of the American Society of Nephrology*, 4(11), 1779–1786.
- Jhamb, M., Pike, F., Ramer, S., Argyropoulos, C., Steel, J., Dew, M. A., ... Unruh, M. (2011). Impact of fatigue on outcomes in the hemodialysis (HEMO) study. *American Journal of Nephrology*, 33(6), 515–523.
- Kangas, M., Bovbjerg, D. H., & Montgomery, G. H. (2008). Cancer-related fatigue: A systematic and meta-analytic review of non-pharmacological therapies for cancer patients. *Psychological Bulletin*, 134(5), 700–741.
- van Kessel, K., & Moss-Morris, R. (2006). Understanding multiple sclerosis fatigue: A synthesis of biological and psychological factors. *Journal of Psychosomatic Research*, 61(5), 583–585.
- van Kessel, K., Moss-Morris, R., Willoughby, E., Chalder, T., Johnson, M. H., & Robinson, E. (2008). A randomized controlled trial of cognitive behavior therapy for multiple sclerosis fatigue. *Psychosomatic Medicine*, 70(2), 205–213.
- Knoop, H., Van Kessel, K., & Moss-Morris, R. (2012). Which cognitions and behaviours mediate the positive effect of cognitive behavioural therapy on fatigue in patients with multiple sclerosis? *Psychological Medicine*, 42(01), 205–213.
- Kontopantelis, E., & Reeves, D. (2009). METAFF: Stata module to perform effect sizes calculations for meta-analysis. *Statistical Software Components*. doi:10.13140/RG.2.1.2747.5282.
- Kosmadakis, G., Bevington, A., Smith, A., Clapp, E., Viana, J., Bishop, N., & Feehally, J. (2010). Physical exercise in patients with severe kidney disease. *Nephron Clinical Practice*, 115(1), c7–c16.
- Koyama, H., Fukuda, S., Shoji, T., Inaba, M., Tsujimoto, Y., Tabata, T., ... Okamura, M. (2010). Fatigue is a predictor for cardiovascular outcomes in patients undergoing hemodialysis. *Clinical Journal of the American Society of Nephrology*, 5(4), 659–666.

- Krupp, L. B., LaRocca, N. G., Muir-Nash, J., & Steinberg, A. D. (1989). The fatigue severity scale: Application to patients with multiple sclerosis and systemic lupus erythematosus. *Archives of Neurology*, 46(10), 1121–1123.
- Lee, B. O., Lin, C. C., Chaboyer, W., Chiang, C. L., & Hung, C. C. (2007). The fatigue experience of haemodialysis patients in Taiwan. *Journal of Clinical Nursing*, 16(2), 407–413.
- Levey, A. S., Coresh, J., Balk, E., Kausz, A. T., Levin, A., Steffes, M. W., ... Eknoyan, G. (2003). National kidney foundation practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. *Annals of Internal Medicine*, 139(2), 137–147.
- Levey, A. S., Eckardt, K.-U., Tsukamoto, Y., Levin, A., Coresh, J., Rossert, J., ... Eknoyan, G. (2005). Definition and classification of chronic kidney disease: A position statement from kidney disease: Improving global outcomes (KDIGO). *Kidney International*, 67(6), 2089–2100.
- Levin, A. (2003). The clinical epidemiology of cardiovascular diseases in chronic kidney disease: Clinical epidemiology of cardiovascular disease in chronic kidney disease prior to dialysis. *Seminars in Dialysis*, 16(2), 101–105.
- Levin, A., Hemmelgarn, B., Culleton, B., Tobe, S., McFarlane, P., Ruzicka, M., ... Madore, F. (2008). Guidelines for the management of chronic kidney disease. *Canadian Medical Association Journal*, 179(11), 1154–1162.
- Michie, S., Richardson, M., Johnston, M., Abraham, C., Francis, J., Hardeman, W., ... Wood, C. E. (2013). The behavior change technique taxonomy (v1) of 93 hierarchically clustered techniques: Building an international consensus for the reporting of behavior change interventions. *Annals of Behavioral Medicine*, 46(1), 81–95.
- Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., & Group, P. (2010). Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *International Journal of Surgery*, 8(5), 336–341.
- Murtagh, F. E., Addington-Hall, J. M., Edmonds, P. M., Donohoe, P., Carey, I., Jenkins, K., & Higginson, I. J. (2007). Symptoms in advanced renal disease: A cross-sectional survey of symptom prevalence in stage 5 chronic kidney disease managed without dialysis. *Journal of Palliative Medicine*, 10(6), 1266–1276.
- Neill, J., Belan, I., & Ried, K. (2006). Effectiveness of non-pharmacological interventions for fatigue in adults with multiple sclerosis, rheumatoid arthritis, or systemic lupus erythematosus: A systematic review. *Journal of Advanced Nursing*, 56(6), 617–635.
- Painter, P., Carlson, L., Carey, S., Paul, S. M., & Myll, J. (2000). Physical functioning and health-related quality-of-life changes with exercise training in hemodialysis patients. *American Journal of Kidney Diseases*, 35(3), 482–492.
- Pawlikowska, T., Chalder, T., Hirsch, S., Wallace, P., Wright, D., & Wessely, S. (1994). Population based study of fatigue and psychological distress. *BMJ*, 308(6931), 763–766.
- Peters, J. L., Sutton, A. J., Jones, D. R., Abrams, K. R., & Rushton, L. (2007). Performance of the trim and fill method in the presence of publication bias and between-study heterogeneity. *Statistics in Medicine*, 26(25), 4544–4562.
- Pildal, J., Hrobjartsson, A., Jørgensen, K., Hilden, J., Altman, D., & Gøtzsche, P. (2007). Impact of allocation concealment on conclusions drawn from meta-analyses of randomized trials. *International Journal of Epidemiology*, 36(4), 847–857.
- Poort, H., Goedendorp, M.M., Peters, M., Bleijenberg, G., Gielissen, M.F.M., Jacobsen, P., ... Knoop, H. (2016). Psychosocial interventions for fatigue during cancer treatment with palliative intent (Protocol). *The Cochrane Library*, (1), 11. doi:10.1002/14651858.CD012030
- Popay, J., Roberts, H., Sowden, A., Petticrew, M., Arai, L., Rodgers, M., ... Duffy, S. (2006). Guidance on the conduct of narrative synthesis in systematic reviews. *ESRC Methods Programme*, 15(1), 047–071.
- Revicki, D. A., Brown, R. E., Feeny, D. H., Henry, D., Teehan, B. P., Rudnick, M. R., & Benz, R. L. (1995). Health-related quality of life associated with recombinant human erythropoietin therapy for predialysis chronic renal disease patients. *American Journal of Kidney Diseases*, 25(4), 548–554.
- Rosenthal, R. (1979). The file drawer problem and tolerance for null results. *Psychological Bulletin*, 86(3), 638–641.
- Rothstein, H. R., Sutton, A. J., & Borenstein, M. (2006). *Publication bias in meta-analysis: Prevention, assessment and adjustments*. Chichester, UK: John Wiley & Sons.
- Schünemann, H., Brozek, J., Oxman, A. (Eds.). (2013). *GRADE handbook for grading quality of evidence and strength of recommendation*. The GRADE Working Group. Available from www.guidelinedevelopment.org/handbook.
- Segura-Ortí, E. (2010). Exercise in haemodialysis patients: A systematic review. *Nefrologia*, 30(2), 236–246.
- Skerrett, T. N., & Moss-Morris, R. (2006). Fatigue and social impairment in multiple sclerosis: The role of patients' cognitive and behavioral responses to their symptoms. *Journal of Psychosomatic Research*, 61(5), 587–593.
- Smart, N., & Steele, M. (2011). Exercise training in haemodialysis patients: A systematic review and meta-analysis. *Nephrology*, 16(7), 626–632.
- Stahl-Timmins, W. (2014). Graphical Overview for Evidence Reviews (GOfER) software. University of Exeter Medical School in association with the PenTAG Health Technology Assessment group and the European Centre for Environment and Human Health.
- Stepanski, E. J., Walker, M. S., Schwartzberg, L. S., Blakely, L. J., Ong, J. C., & Houts, A. C. (2009). The relation of trouble sleeping, depressed mood, pain, and fatigue in patients with cancer. *Journal of Clinical Sleep Medicine*, 5(2), 132–136.
- Sterne, J. A., Sutton, A. J., Ioannidis, J., Terrin, N., Jones, D. R., Lau, J., ... Schmid, C. H. (2011). Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ*, 343, d4002–d4002.

- Storer, T. W., Casaburi, R., Sawelson, S., & Kopple, J. D. (2005). Endurance exercise training during haemodialysis improves strength, power, fatigability and physical performance in maintenance haemodialysis patients. *Nephrology Dialysis Transplantation*, 20(7), 1429–1437.
- Terrin, N., Schmid, C. H., Lau, J., & Olkin, I. (2003). Adjusting for publication bias in the presence of heterogeneity. *Statistics in Medicine*, 22(13), 2113–2126.
- Tobias, A. (1999). Assessing the influence of a single study in the meta-analysis estimate. *Stata Technical Bulletin*, 8(47), 1–48.
- van Vilsteren, M. C., de Greef, M. H., & Huisman, R. M. (2005). The effects of a low-to-moderate intensity pre-conditioning exercise programme linked with exercise counselling for sedentary haemodialysis patients in The Netherlands: Results of a randomized clinical trial. *Nephrology Dialysis Transplantation*, 20(1), 141–146.
- Walker, E., Hernandez, A. V., & Kattan, M. W. (2008). Meta-analysis: Its strengths and limitations. *Cleveland Clinic Journal of Medicine*, 75(6), 431–439.
- Ware, J., Snow, K., Kosinski, M., & Gandek, B. (1993). *SF-36 health survey: Manual and interpretive guide*. Boston, MA: The Health Institute, New England Medical Center.
- Ware Jr, J. E., & Sherbourne, C. D. (1992). The MOS 36-item short-form health survey (SF-36): I. Conceptual framework and item selection. *Medical Care*, 30, 473–483.
- Weisbord, S. D., Fried, L. F., Mor, M. K., Resnick, A. L., Unruh, M. L., Palevsky, P. M., ... Kimmel, P. L. (2007). Renal provider recognition of symptoms in patients on maintenance hemodialysis. *Clinical Journal of the American Society of Nephrology*, 2(5), 960–967.
- van der Werf, S., Evers, A., Jongen, P. J., & Bleijenberg, G. (2003). The role of helplessness as mediator between neurological disability, emotional instability, experienced fatigue and depression in patients with multiple sclerosis. *Multiple Sclerosis*, 9(1), 89–94.
- White, P. D., Goldsmith, K. A., Johnson, A. L., Potts, L., Walwyn, R., DeCesare, J. C., ... Cox, D. (2011). Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): A randomised trial. *The Lancet*, 377(9768), 823–836.
- Wiborg, J. F., Knoop, H., Prins, J. B., & Bleijenberg, G. (2011). Does a decrease in avoidance behavior and focusing on fatigue mediate the effect of cognitive behavior therapy for chronic fatigue syndrome? *Journal of Psychosomatic Research*, 70(4), 306–310.